# הודעה על החמרה ( מידע בטיחות) בעלון לרופא

תאריך: ‏

שם תכשיר באנגלית ומספר רישום: Isoflurane USP, Terrell ™ 105 52 28997 00

שם בעל הרישום: Pharma Medis Ltd.

טופס זה מיועד לפרוט ההחמרות בלבד !

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| **פרק בעלון** | **עלון מקורי** | **עלון חדש** |
| **Special Warnings and Precautions for Use** | Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.Isoflurane, like some other inhalational anesthetics, can react with desiccated carbon dioxide (CO2) absorbents to produce carbon monoxide which may result in elevated levels of carboxyhemoglobin in some patients. Case reports suggest that barium hydroxide lime and soda lime become desiccated when fresh gases are passed through the CO2 absorber canister at high flow rates over many hours or days. When a clinician suspects that CO2 absorbent may be desiccated, it should be replaced before the administration of isoflurane.During marketing, there have been rare reports of mild, moderate and severe (some fatal)post-operative hepatic dysfunction. The causal relationship is unknown.Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.**CLINICAL PHARMACOLOGY**The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BEMONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, althoughthe frequency is less than with enflurane.anesthesia is deepened.**CLINICAL PHARMACOLOGY** Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. | Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering isoflurane to patients at risk for QT prolongation. Caution should be exercised in administering general anaesthesia, including isoflurane, to patients with mitochondrial disorders. Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Clinical judgement should be observed when using isoflurane during obstetric anaesthesia. Consideration should be taken to use the lowest possible concentration of isoflurane in obstetrical operations (please refer to section 4.6). Rare cases of extreme heat, smoke and/or spontaneous fire in the anaesthesia machine have been reported during the administration of general anaesthesia with drugs in this class when used in conjunction with desiccated CO2 absorbents, specifically those containing potassium hydroxide (e.g. Baralyme). When a clinician suspects that the CO2 absorbent may be desiccated, it should be replaced before administration of isoflurane. The colour indicator of most CO2 absorbents does not necessarily change as a result of desiccation. Therefore, the lack of significant colour change should not be taken as an assurance of adequate hydration. CO2 absorbents should be replaced routinely regardless of the state of the colour indicator. **General** It has been reported that previous exposure to halogenated hydrocarbon anaesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury. Cirrhosis, viral hepatitis or other pre-existing liver disease can be a reason to select an anaesthetic other than a halogenated anaesthetic. Isoflurane must be used with caution in patients with increased intracranial pressure. In such cases hyperventilation may be necessary.Use of isoflurane in hypovolaemic, hypotensive and debilitated patients has not been extensively investigated. A lower concentration of isoflurane is recommended for use in these patients. Isoflurane may cause a slight decrease in intellectual function for 2-4 days following anaesthesia. Small changes in moods and symptoms may persist for up to 6 days after administration. This must be taken into account when patients resume normal daily activities, including driving or operating heavy machinery (please refer to section 4.7). A potentiation of neuromuscular fatigue can be seen in patients with neuromuscular diseases, such as myasthenia gravis. Isoflurane should be used with caution in these patients. Isoflurane should be administered with caution to patients who can develop bronchoconstriction since bronchospasm can occur (see section 4.8). Isoflurane may cause respiratory depression which may be augmented by narcotic premedication or other agents causing respiratory depression. During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children (see section 4.8). ***Children Under Two Years of Age*** Caution should be exercised when isoflurane is used in small children due to limited experience with this patient-group. ***Malignant Hyperthermia*** There have been postmarketing reports of malignant hyperthermia. Some of these reports have been fatal. ***Perioperative hyperkalaemia*** Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine kinase levels and in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.   |
| 4.5 Interactions with Other medicinal products and Other Forms of Interaction  | Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N2O. (See CLINICAL PHARMACOLOGY). | *Combinations advised against:* Beta-sympathomimetic agents like isoprenaline and alpha- and beta- sympathomimetic agents like adrenaline and noradrenaline should be used with caution during isoflurane narcosis, due to a potential risk of ventricular arrhythmia. Non-selective MAO-inhibitors: Risk of crisis during the operation. Treatment should be stopped 15 days prior to surgery. *Combinations requiring precautions in using:* Indirect-acting sympathomimetics (amphetamines and their derivatives, psychostimulants, appetite suppressants, ephedrine and its derivatives): Risk of perioperative hypertension. In patients undergoing elective surgery, treatment should ideally be discontinued several days before surgery. Adrenaline, by subcutaneous or gingival injections: risk of serious ventricular arrhythmia as a consequence of increased heart rate, although the myocardial sensitivity with respect to adrenaline is lower with the use of isoflurane than in the case of halothane. Cardiovascular compensation reactions may be impaired by beta-blockers. *Inducers of CYP2E1* Medicinal products and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of isoflurane and lead to significant increases in plasma fluoride concentrations. Use of isoflurane and isoniazid can increase the risk of potentiation of the hepatotoxic effects. Calcium antagonists, in particular dihydropyridine derivates: isoflurane may lead to marked hypotension in patients treated with calcium antagonists. Caution should be exercised when calcium antagonists are used concomitantly with inhalation anaesthetics due to the risk of additive negative inotropic effect. Opioids, benzodiazepines and other sedative agents are associated with respiratory depression, and caution should be exercised when concomitantly administered with isoflurane Concomitant use of succinylcholine with inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients during the post-operative period. All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with non-depolarizing agents. Neostigmine has an effect on the non-depolarising relaxants, but has no effect on the relaxing action of isoflurane itself. MAC (minimum alveolar concentration) is reduced by concomitant administration of N2O in adults (see section 4.2).  |
| **4.6 Fertility, pregnancy and lactation**  |  | ***Use in Caesarean Section***Isoflurane, in concentrations up to 0.75%, has been shown to be safe for the maintenance of anaesthesia for caesarean section (please refer to section 4.4). |
| **4.7 Effects on Ability to Drive and Use Machines**  |  | Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for 2-4 days after anaesthesia with isoflurane. As with other anaesthetics, small changes in moods and symptoms may persist for up to 6 days after administration (see Section 4.4).  |
| **Undesirable Effects**  | Adverse reactions encountered in the administration of isoflurane are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.Shivering, nausea, omiting and ileus have been observed in the postoperative period. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress. See PRECAUTIONS for information regarding malignant hyperthermia.During marketing, there have been rare reports of mild, moderate and severe (some fatal)post-operative hepatic dysfunction. The causal relationship is unknown. | ***a. Summary of the safety profile***  Potential serious undesirable effects include malignant hyperthermia, hyperkalaemia, elevated serum creatine kinase, myoglobinuria, anaphylactic reactions and liver adverse reactions (please refer to section 4.4 and 4.8). Shivering, nausea, vomiting, ileus, agitation and delirium have been observed in the post-operative period. Cardiac arrest, bradycardia and tachycardia have been observed with general inhalation anaesthetic drugs including isoflurane. Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal) have been received. ***b. Tabulated summary of adverse reactions*** The following table displays adverse reactions reported in clinical trials and from postmarketing experience. Frequency cannot be estimated from the available data, therefore it is “not known”. **(See appendix no 1).** ***c. Description of selected adverse reactions*** Transient increases in blood bilirubin, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed. As with other general anaesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress. Rare reports of hypersensitivity (including dermatitis contact, rash, dyspnoea, wheezing, chest discomfort, swelling face, or anaphylactic reaction) have been received, especially in association with long-term occupational exposure to inhaled anaesthetic agents, including isoflurane. These reactions have been confirmed by clinical testing (e.g., methacholine challenge). The etiology of anaphylactic reactions experienced during inhalational anaesthetic exposure is, however, unclear because of the exposure to multiple concomitant drugs, many of which are known to cause such reactions. Minimally raised levels of serum inorganic fluoride occur during and after isoflurane anaesthesia, due to biodegradation of the agent. It is unlikely that the low levels of serum inorganic fluoride observed (mean 4.4 µmol/l in one study) could cause renal toxicity, as these are well below the proposed threshold levels for kidney toxicity. ***d. Paediatric population*** Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. (See section 4.4.) During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm. (See section 4.4.) ***e. Other special populations* Neuromuscular disease:** Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease (see section 4.4). **Elderly:** Lesser concentrations of isoflurane are normally required to maintain surgical anaesthesia in elderly patients. (See section 4.2.).  |
| **4.9 Overdose**  | In the event of overdosage, or what may appear to be overdosage, the fqllowing actionshould be taken:Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen. | As with other halogenated anaesthetics, hypotension and respiratory depression have been observed. Close monitoring of blood pressure and respiration is recommended. Supportive measures may be necessary to correct hypotension and respiratory depression resulting from excessively deep levels of anaesthesia. |

**מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות בצהוב**

שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

**הועבר בדואר אלקטרוני בתאריך\_\_\_1.11.17\_\_**

* כל השינויים עולים בקנה אחד עם תנאי הרישום (תעודת הרישום, תעודת האיכות וטופס פרטי תכשיר העדכני)
* כל הכתוב בהצעת העלון, תואם את תנאי הרישום.
* קיים עלון לצרכן והוא מעודכן בהתאם.
* אסמכתא לבקשה: \_\_עלון תכשיר המקור Forane המאושר בישראל \_

**האסמכתא מצ"ב**.

* השינוי הנ"ל אושר על ידי רשויות הבריאות ב\_ישראל \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
* אני, הרוקח הממונה של חברת \_\_פארמה מדיס בע"מ\_\_\_\_\_\_ מצהיר בזה כי אין שינויים נוספים , מלבד אלה שסומנו בהצעת העלון.
* אני מצהיר כי השינויים אינם יוצרים סתירה פנימית במידע בעלון.

עלון זה לא מטופל במקביל במסגרת אחרת (כגון: עדכון עלון במסגרת בקשה לתוספת התוויה, החמרה וכו') . במידה וקיים טיפול מקביל במסגרת אחרת- יש לציין זאת.

חתימת הרוקח הממונה (שם וחתימה)\_\_\_\_\_אבנר דור \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**נספח מס 1**

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| **SUMMARY OF MOST FREQUENT ADVERSE DRUG REACTIONS** |
| **SOC**  | **FREQUENCY**  | **ADVERSE REACTIONS**  |
| Blood and lymphatic system disorders  | Not known  | Carboxyhaemoglobinaemia2 |
| Immune system disorder  | Not known Not known  | Anaphylactic reaction1Hypersensitivity1 |
| Metabolism and nutrition disorders  | Not known Not known  | Hyperkalaemia2Blood glucose increased  |
| Psychiatric disorders  | Not known Not known Not known  | Agitation Delirium Mood altered5 |
| Nervous system disorders | Not known Not known  | Convulsion Mental impairment4 |
| Cardiac disorders  | Not known Not known Not known Not known Not known  Not known  | Arrhythmia BradycardiaCardiac arrest Electrocardiogram QT prolonged Tachycardia Torsade de pointes |
| Vascular disorders  | Not known Not known  | Hypotension2Haemorrhage3 |
| Respiratory, thoracic and mediastinal disorders  | Not known Not known Not known Not known Not known  | Bronchospasm2Dyspnoea1 Wheezing1 Respiratory depression2Laryngospasm2  |
| Gastrointestinal disorders  | Not known Not known Not known  | Ileus Vomiting Nausea  |
| Hepatobiliary disorders  | Not known Not known Not known  | Hepatic necrosis2Hepatocellular injury2Blood bilirubin increased  |
| Skin and subcutaneous tissue disorders  | Not known Not known Not known  | Swelling face1Dermatitis contact1Rash1 |
| Renal and urinary disorders  | Not known Not known  | Blood creatinine increased Blood urea decreased  |
| General disorders and  | Not known  | Hyperthermia malignant2 |
| administration site conditions  | Not known Not known  | Chest discomfort1Chills  |
| Investigations  | Not known Not known Not known Not known Not known Not known  | White blood cell count increased1 Hepatic enzyme increased2Fluoride increased1 Electroencephalogram abnormal Blood cholesterol decreased Blood alkaline phosphatase decreased  |
| Musculoskeletal and connective tissue disorders  | Not known Not known  | Myoglobinuria Rhabdomyolysis  |

1. See section 4.8(c)
2. See section 4.4
3. In patients undergoing induced abortion. See section 4.4.
4. May cause a slight decrease in intellectual function for 2-4 days after anaesthesia. See section 4.4.
5. Small changes in moods and symptoms may persist for up to 6 days. See section 4.4.